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Digest Paper

Catalytic asymmetric reactions in alkaloid and terpenoid syntheses

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ABSTRACT

Catalytic asymmetric induction is one of the most important methods in current synthetic organic chemistry for designing efficient and attractive synthetic routes. The efficient total synthesis of a natural product can be achieved through the identification of appropriate method and strategy. This Letter introduces the catalytic asymmetric syntheses of alkaloids and terpenoids based on an overview of four recently reported types of asymmetric reaction: (1) asymmetric decarboxylative allylation, (2) organocatalytic cascade reaction, (3) polyene cyclization, and (4) asymmetric [2+2]-photocycloaddition catalyzed by a chiral Lewis acid.

Contents

Introduction

Novel natural products that display attractive bioactivities have been isolated from a variety of natural resources. The structural determination of these natural products has been accelerated recently through the development of a range of instrumental and analytical techniques. Natural resources play an important role in the search for biologically active compounds in the field of pharmaceuticals and agrochemicals;[1] however, the isolation of an attractive bioactive compound as a minor component in nature typically does not allow for the elucidation of its biological mode of action or for the development of a pharmaceutical or agrochemical product without the establishment of a supply method. One solution to this problem is presented by natural product synthesis methods using synthetic organic chemistry. Such methods are an indispensable research field.

In the past, the efficiency of a target molecule synthesis tended to receive little attention as researchers worked toward the fastest route to total synthesis; however, the realization of a sustainable society[2] requires the development of effective synthetic routes to natural products that utilize limited resources efficiently in addition to achieving total synthesis. Several measures of a synthetic route's efficiency have been proposed, including the atom economy,[3] redox economy,[4] and step economy,[5] and several total syntheses focusing on efficiency have been reported.[6] In general, synthetic strategies are planned using a retrosynthetic analysis upon initiating the total synthesis of a target molecule. When considering a synthetic route for a complex natural product, many possible retrosynthetic analyses are available. The key to achieving an efficient total synthesis lies in selecting the most appropriate synthetic route based on a variety of retrosynthetic considerations. Asymmetric reactions are indispensable when the selective preparation of one enantiomer of a target molecule must be performed. Because each enantiomer of a certain biologically active compound

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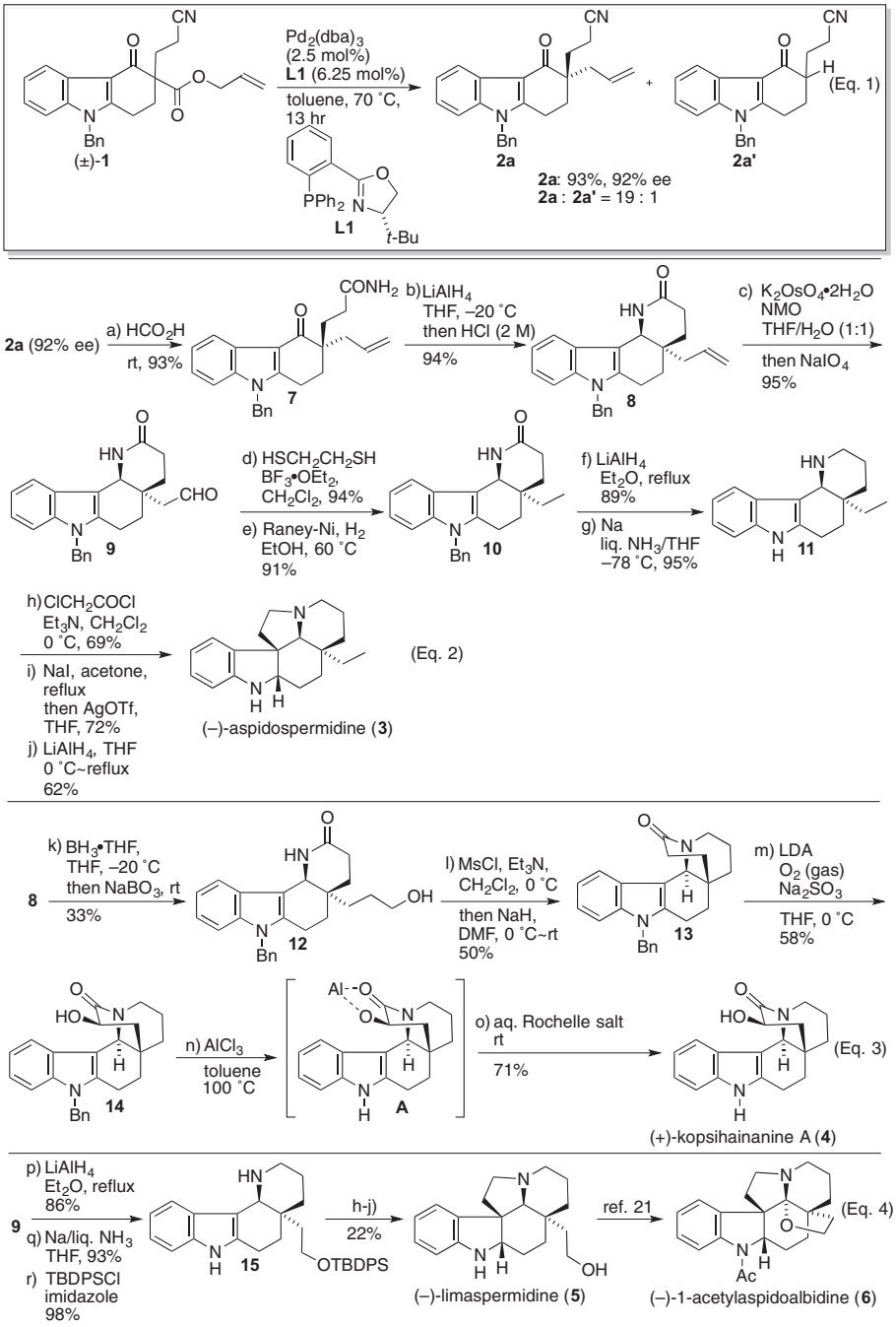
can display distinct effects, new methods for asymmetric synthesis have remained under active development. Asymmetric synthesis may be divided roughly into four categories:[7] the chiral pool method;[8] optical resolution;[9] the use of chiral auxiliaries;[10] and the use of a chiral catalyst.[11] Recently, asymmetric reactions that rely on the memory of chirality (MOC), in which asymmetric induction occurs via a chiral enolate intermediate with a lifetime in its chirality, have been applied in natural product synthesis.[12] These reactions play significantly important roles in the total synthesis of natural products. Among these reactions, the catalytic asymmetric reactions have several advantages for natural product synthesis: compared to the chiral pool method, any starting materials may be selected because an achiral compound can be used. Catalytic asymmetric reactions can shorten a synthetic route relative to a route based on the use of chiral auxiliaries because asymmetric induction proceeds from the chirality of the catalysis reaction. Theoretically, a chiral compound may be obtained in quantitative chemical yield compared to the optical resolution. However, in some cases, catalytic asymmetric reactions put synthetic chemists into trouble if the asymmetric induction cannot occur efficiently due to the narrow and limited scope of the catalyst's substrates, due to reconsideration of the substrates or the synthetic route, or due to the inability to improve the enantioselectivity. In these cases, strict optimization of reaction conditions is then required to improve the enantiomeric excess. Synthetic chemists must choose an appropriate catalytic asymmetric reaction to achieve the effective total synthesis of a natural product by assessing these merits and drawbacks.

This review provides an overview of recent attractive and interesting reports of catalytic asymmetric total syntheses of alkaloids and terpenoids. Asymmetric dihydroxylation,[13] asymmetric epoxidation,[14] and asymmetric hydrogenation[15] are frequently applied to enantioselective total synthesis of natural products not only because their experimental procedures are simple and versatile, but also because the chemical yield and optical purity resulting from these reactions are relatively highly reproducible. This discussion will focus on enantioselective total syntheses using several recently developed asymmetric catalytic reactions that are distinct from these famous reactions.

Total synthesis of aspidosperma alkaloids using asymmetric decarboxylative allylation

Terpenoid indole alkaloids make up a major fraction of the alkaloids present in plants, and more than 3000 such alkaloids have been recognized.[16] Several synthetic studies of these alkaloids have been reported because most of them have complex and interesting chemical structures and show attractive biological activities.[16] One such class of alkaloids, the aspidosperma alkaloids, includes a quaternary carbon in their ring-fused structure. A key to the successful achievement of an effective total synthesis of the aspidosperma alkaloids is to select an appropriate strategy for constructing the quaternary stereogenic center. Catalytic asymmetric decarboxylative allylation is often applied in the total synthesis of natural products bearing a quaternary carbon[17] because these reactions present a powerful tool for the effective and highly enantioselective construction of quaternary stereogenic centers. Recently, Shao and co-workers reported the total syntheses of aspidosperma alkaloids using a key intermediate prepared by the asymmetric decarboxylative allylation of carbazolone derivatives.[18a–c] The decarboxylative allylation of carbazolone derivatives presents a significant challenge, unlike the corresponding reaction of the β-ketoester derivatives, because the nucleophilicity at the indole C(3) can affect the decarboxylative allylation. Shao and co-workers investigated a catalytic asymmetric decarboxylative allylation using carbazolone derivative **1** (Scheme 1, Eq. 1).[18a] While investigating the optimized conditions through the use of a variety of chiral ligands, they found that treatment of **1** in the presence of $Pd_2(dba)_3$ and phosphinooxazoline ligand **L1** in toluene gave desired compound **2a** in 93% yield and in 92% ee with the concomitant formation of small amounts of **2a′** as a side product of the deallyloxycarbonyl reaction. The optimal conditions provided carbazole derivatives containing a variety of substituents at the quaternary stereogenic center α to the ketone in up to 97% ee. The total syntheses of (−)-aspidospermidine (**3**), (+)-kopsihainanine A (**4**), and (−)-limaspermidine (**5**), and the formal total synthesis of (−)-1-acetylaspidoalbidine (**6**) were accomplished from **2a** (Scheme 1, Eqs. 2–4).[18a,b] The conversion of **2a** into amide **7** under acidic conditions, followed by the chemoselective reduction at the keto carbonyl group and the intramolecular cyclization under acidic conditions, between the benzylic secondary alcohol and amide, gave **8** (Scheme 1, Eq. 2). Oxidative degradation at the vinyl group led to aldehyde **9** and its thioacetal formation followed by desulfurization in the presence of a Raney-Ni catalyst under hydrogen provided **10**. The reduction of **10** with $LiAlH_4$ and debenzylation under Birch conditions gave the key intermediate **11**, which was converted to (−)-aspidospermidine (**3**) in three steps, as reported by Heathcock and co-workers:[19] (1) *N*-chloroacetylation, (2) formation of the γ-lactam, and (3) reduction of amide. Synthesis of (+)-kopsihainanine A (**4**) was commenced from **8** (Scheme 1, Eq. 3). Hydroboration of **8** and oxidative treatment gave alcohol **12**. *O*-mesylation of **12** followed by intramolecular *N*-alkylation under basic conditions led to **13**. Amide **13** was converted into (+)-kopsihainanine A (**4**) through known methods, a stereoselective α-hydroxylation followed by *N*-debenzylation, as reported by Xie, She, and co-workers;[20] however, it was not clear whether the synthetic **4** was identical to the natural compound because the synthetic **4** was not soluble in chloroform (although it was soluble in DMSO), whereas the natural **4** was soluble in chloroform. After several analyses and investigations, they speculated that the product of the debenzylation of **14** with aluminum chloride was the chelate compound **A** in complex with aluminum. The pure synthetic **4** was obtained through the addition of Rochelle salt in a workup of the debenzylation with aluminum chloride. The synthesis of (−)-limaspermidine (**5**) was begun from **9** (Scheme 1, Eq. 4).[18c] The reduction of aldehyde and amide moieties in **9**, followed by the debenzylation and protection of the primary alcohol with a *tert*-butyldiphenylsilyl group, gave **15**, which led to **5** using a sequence similar to those applied to obtain **3** from **11** in the (−)-aspidospermidine synthesis. The conversion of **5** into **6** was reported in two steps,[21] so the formal synthesis of **6** was also achieved. Using catalytic asymmetric decarboxylative allylation, Shao and co-workers recently reported the total syntheses of (+)-10-oxocylindrocarpidine, (+)-cylindrocarpidine, (−)-*N*-acetylcylindrocarpinol, and (+)-aspidospermine.[18c]

Zhu and co-workers reported the total syntheses of five terpenoid indole alkaloids:[22] (−)-mersicarpine (**18**), (−)-scholarisine G (**19**), (+)-melodinine E (**20**), (−)-leuconoxine (**21**), and (−)-leuconolam (**22**), from the key intermediate **17** (90% yield, 92% ee), which was prepared from β-ketoester **16** using a catalytic asymmetric decarboxylative allylation developed by Stoltz (Scheme 2).[23] The key to these total syntheses was that the nucleophilic addition of the nitrogen (N(4)) residue occurred selectively via discrimination between the two carbonyl carbons (C(7) and C(21) positions) in **23**, thereby controlling their electrophilicities. Ozonolysis of cyclohexenone **24**, which was converted from **17** in four steps, including functionalization at the residual chain and α-arylation, gave α-diketone **23**. Hydrogenolysis in the presence of Pd/C under a H_2 atmosphere, followed by the sequential treatment with KOH in ethanol, with molecular oxygen, and with dimethyl sulfide in the same flask, gave (−)-mersicarpine (**18**) in 75% yield (Scheme 2, Eq. 1). In this one-pot reaction, it was assumed that the sequential

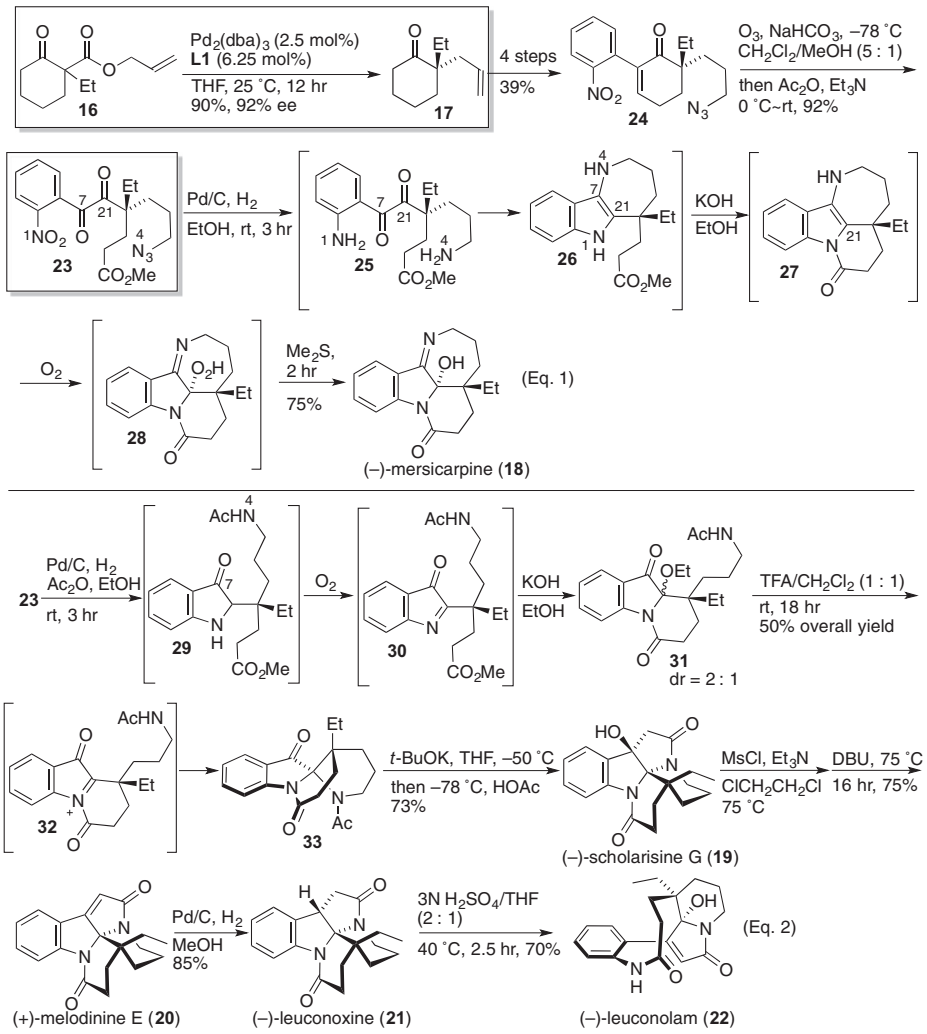


Scheme 1. Catalytic asymmetric decarboxylative allylation of carbazolone (Eq. 1) and total syntheses of aspidosperma alkaloids (Eqs. 2–4).

reactions proceeded through the reduction of azide and nitro groups of **23**, bond formation between N(1) and C(21) and between N(4) and C(7) to give **26**, lactamization of **26** under basic conditions, oxidation of **27** with molecular oxygen, and reduction of peroxide **28** by dimethyl sulfide. Next, the syntheses of (−)-scholarisine G (**19**), (+)-melodinine E (**20**), (−)-leuconoxine (**21**), and (−)-leuconolam (**22**) commenced from **23** (Scheme 2, Eq. 2). Hydrogenolysis of **23** in the presence of acetic anhydride gave *N*-acetylated **29**. Under these conditions, intramolecular cyclization between N(4) and C(7) was prevented because the nucleophilicity of nitrogen was decreased by *N*-acetylation. Direct oxidation of **29** without isolation gave unstable indol-3-one **30**, which was treated with KOH in ethanol to afford a 2/1 diastereomeric mixture of **31**. Cyclization of **31** with trifluoroacetic acid (TFA) in dichloromethane proceeded via the *N*-acyliminium intermediate **32** to give **33**. Finally, an intramolecular aldol reaction with *tert*-BuOK gave (−)-scholarisine G (**19**). From **19**, the syntheses of (+)-melodinine E (**20**), (−)-leuconoxine (**21**), and (−)-leuconolam (**22**) were achieved through a two-step dehydration reaction from **19**, reduction of the olefin in the cyclopentenone moiety of **20**, and a ring-opening reaction of aminal **21** under acidic conditions, respectively.

Total synthesis of alkaloids using organocatalytic cascade reactions

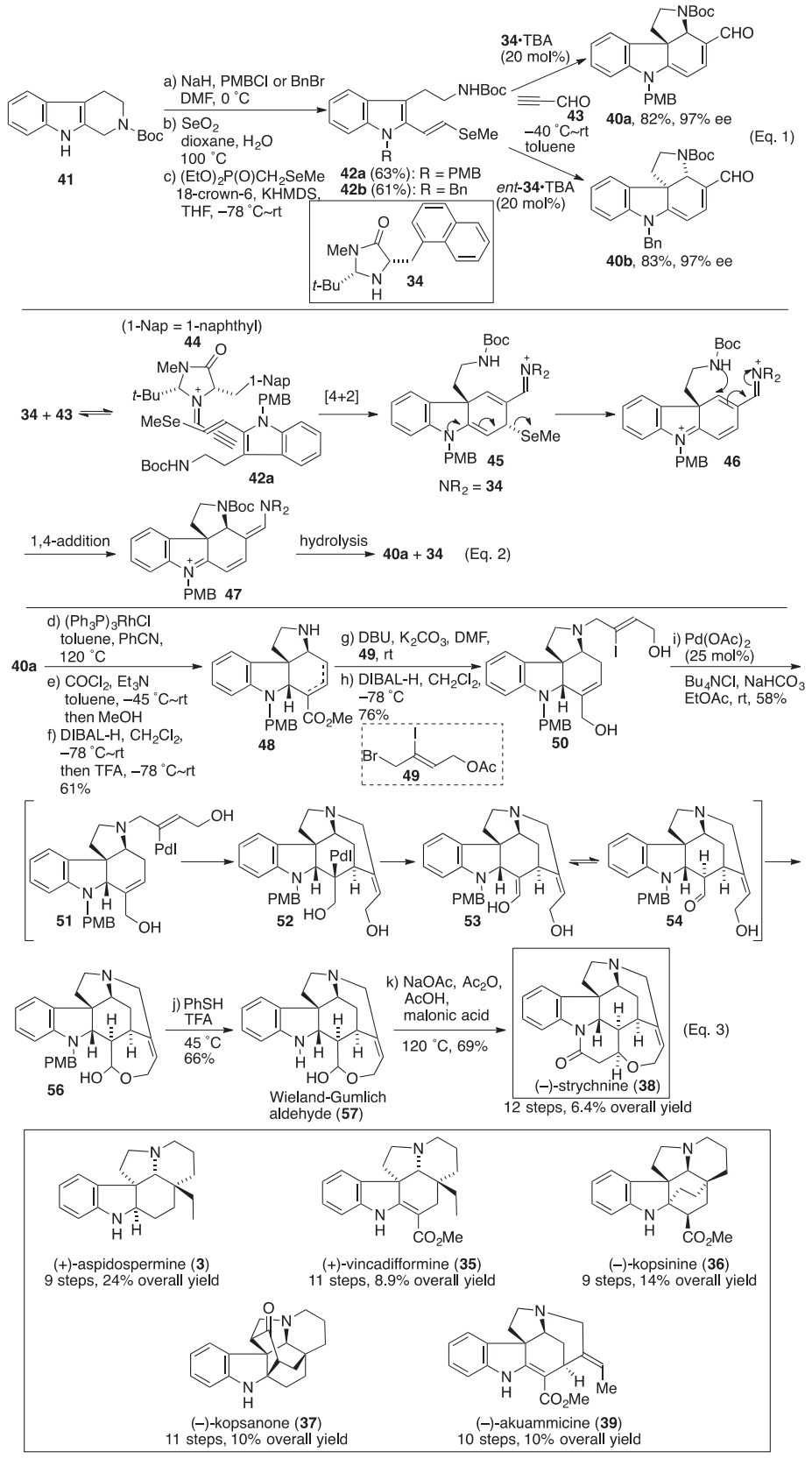
Asymmetric organocatalytic reactions[11a–g] are frequently employed in the total synthesis of natural products along with metal catalysts consisting of chiral ligands and a transition metal.



Scheme 2. Asymmetric syntheses of (−)-mersicarpine (**18**) (Eq. 1), (−)-scholarisine G (**19**), (+)-melodinine E (**20**), (−)-leuconoxine (**21**), and (−)-leuconolam (**22**) (Eq. 2) using asymmetric decarboxylative allylation.

Few organocatalytic asymmetric reactions have been developed over the past 30 years, when the first asymmetric Robinson annulation reaction catalyzed by proline was reported;[24] however, the development of asymmetric organocatalytic reactions has attracted significant attention, including the asymmetric aldol reaction reported by List and co-workers in 2000[25] and the various asymmetric reactions that employ unique and effective organocatalysts. MacMillan and co-workers achieved the total syntheses of (+)-aspidospermidine ((+)-**3**), (+)-vincadifformine (**35**), (−)-kopsinine (**36**), (−)-kopsanone (**37**), (−)-strychnine (**38**), and (−)-akuammicine (**39**)[26] using the imidazolidinone catalyst **34**, originally developed by MacMillan's group. These terpenoid indole alkaloids are divided into aspidosperma types, including **3** and **35**–**37**, and corynanthe types, including **38** and **39**.[16] The alkaloids are categorized according to the rearrangement pattern in the secologanin moiety derived from terpene. While planning a synthesis of a natural product and its various congeners, a divergent synthesis from a key intermediate bearing the main scaffold of the natural product would be general and effective. Shao and Zhu have synthesized several congeners from key intermediates. This methodology is frequently applied to the synthesis of related congeners but is rarely used for the synthesis of different families, for example, the synthesis of aspidosperma-type and corynanthe-type compounds from the same key intermediate. Focusing on these points, MacMillan and co-workers synthesized aspidosperma-type and corynanthe-type alkaloids from similar key intermediates **40a** and **40b**, appropriately functionalized (Scheme 3, Eq. 1). Carbazole derivative **40a** was prepared in 82% yield and in 97% ee from **42a** (R = PMB), which was derived from **41** in three steps, by treatment with propynal (**43**) in the presence of catalytic amounts of the tribromoacetic acid salt of **34** (**34**·TBA). The main process of this reaction was thought to proceed through a cascade reaction consisting of asymmetric intermolecular Diels–Alder reactions and a sequential intramolecular conjugate addition reaction catalyzed by **34** (Scheme 3, Eq. 2). Namely, iminium **44**, which was generated from the condensation of **34** and **43**, underwent an *endo*-selective intermolecular Diels–Alder reaction with **42a** to give **45**, β-elimination of methyl selenide from **45** then gave **46**. An intramolecular conjugate addition reaction of **46** via several processes afforded the pyrrolidine-ring-forming **47**. Finally, recycle of **34** proceeded through the hydrolysis of **47** with the concomitant release of **40a**.

The total synthesis of (−)-strychnine (**38**) from **40a** is shown in Scheme 3, Eq. 3 as a representative synthesis of congeners. After decarbonylation of **40a** in the presence of the Wilkinson catalyst, the methoxycarbonyl group was installed at the α position of dienamine by treating with phosgene and methanol. The stereoselective reduction of enamine, obtained through methoxycarbonylation, with diisobutylaluminum hydride (DIBAL-H) gave an olefinic regioisomeric mixture of **48** in 61% yield in three steps. *N*-allylation of **48** with **49** using DBU followed by the simultaneous reduction of ester



Scheme 3. Organocatalytic cascade reactions (Eqs. 1 and 2) and the shortest synthesis of (−)-strychnine (**38**) using the key intermediate **40a** (Eq. 3).

and deprotection of the acetyl group with DIBAL-H gave allylic alcohol **50** as a sole product. Isomerization of the olefin occurred at the allylation step due to the basic conditions. The contiguous Jeffery–Heck cyclization/lactol formation reaction of **50** gave **56**, which was converted into Wieland–Gumlich aldehyde (**57**) by deprotection of the PMB group. Conversion of **50** into **56** occurred in the

following reaction sequence: (1) insertion of Pd(0) into vinyl iodide **50** gave **51**, which underwent carbopalladation to give alkylpalladium intermediate **52**, which formed a six-membered ring; (2) after conversion into enol **53** through β-elimination from **52**, the hydroxyl group proximal to enol moiety formed a lactol. The total synthesis of (−)-strychnine (**38**) was accomplished by the treatment of **57** with malonic acid, acetic anhydride, acetic acid, and sodium acetate. The authors mentioned that this total synthesis had been achieved in 6.4% yield in 12 steps, and this approach offered the shortest synthetic route among those reported previously. The other 5 alkaloids were also synthesized in 8.9–24% yields in 9–11 steps using the key intermediates **40a** or **40b**.

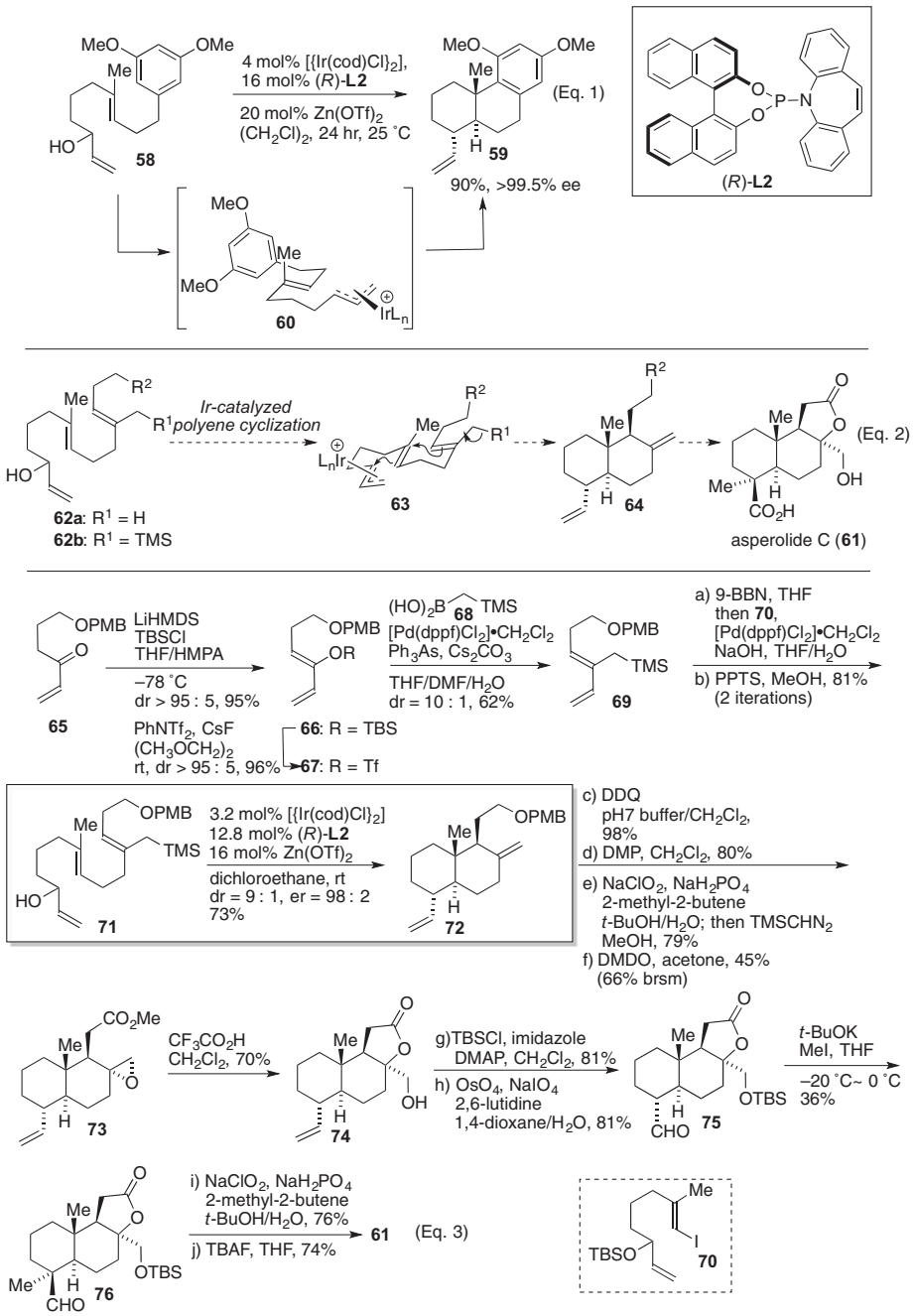
Synthesis of terpenoids using enantioselective polyene cyclization

Terpenoids are derived from monoterpene, which is a dimer of isoprene (C5) units bonded in a head-to-tail fashion. Divergent structural motifs may be present in this class of compounds.[16] The chiral polycyclic terpenoids consisting of 6-membered rings are thought to be biosynthetically produced from farnesyl diphosphate (C15), geranyl geranyl diphosphate (C20), geranyl farnesyl diphosphate (C25), or squalene (C30) via a cationic intermediate generated enzymatically through asymmetric protonation via a contiguous polyene cyclization.[16,27] Although many synthetic methods for preparing polycyclic compounds based on the proposed biosynthesis have been developed,[28] relatively few reports have applied this method to natural product synthesis.[29] The Carreira[29c] and Corey[29d] groups recently reported a natural product synthesis that employed an enantioselective polyene cyclization.

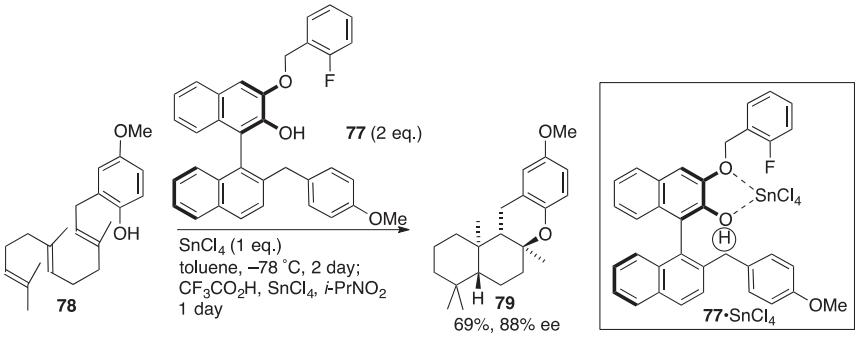
Carreira and co-workers developed a variety of enantioselective transformations in the presence of catalytic amounts of a chiral iridium complex.[30] These reactions include the enantioselective polyene cyclization of the inactivated allylic alcohol in the presence of an iridium complex (Scheme 4, Eq. 1).[30c] The catalytic enantioselective polyene cyclization of **58** with a chiral iridium complex formed from the chiral ligand **L2** proceeds by addition of $Zn(OTf)_2$, which acts as an activator of the allylic alcohol to give the cyclized compound **59** in 90% yield and in more than 99.5% ee. This reaction is expected to proceed through the formation of allyliridium intermediate **60** derived from allylic alcohol **58** activated by $Zn(OTf)_2$ and the iridium catalyst. Highly electrophilic arenes may be introduced at the ends of a polyene to effectively terminate this cationic cascade reaction. An investigation of the arenyl substituents revealed that 3,4-dimethoxyphenyl, 3-methoxyphenyl, *N*-protected pyrrole and indole, and benzofuran groups were tolerated in this cyclization. Carreira and co-workers applied this method to the total synthesis of asperolide C (**61**) (Scheme 4, Eq. 2).[29c] The triene **62a** (R^1 = H) was proposed as a precursor for an asymmetric polyene cyclization because **61** does not include an arenyl substituent in its structure; however, because triene **62a** is expected to provide a lower electrophilicity compared with the substrate bearing an arenyl substituent, the polyene cyclization may not proceed effectively. These considerations led the selection of the allylsilane **62b** (R^1 = TMS) as a precursor, because the polyene cyclization was expected to proceed effectively due to the β-effects of the silane[31] and because functionalization after cyclization was expected to proceed easily. Vinyl ketone **65** derived from γ-butyrolactone in three steps was treated with lithium hexamethyldisilazide (LiHMDS) and TBSCl to give silyl enol ether **66**, which was converted into enol triflate **67** through the use of CsF and $PhNTf_2$ (Scheme 4, Eq. 3). The direct conversion of **65** into **67** was problematic; therefore, the two-step conversion described above was employed. The coupling reaction between **68** and **67**, catalyzed by $[Pd(dppf)Cl_2]\cdot CH_2Cl_2$ and Ph_3As, gave the allylsilane **69**, which led to the precursor **71** for the asymmetric polyene cyclization via regioselective hydroboration of **69**, followed by Suzuki coupling with **70** and the sequential desilylation. The key enantioselective polyene cyclization reaction was performed through the use of **71**. That is, the treatment of **71** in the presence of 3.2 mol % $[\{Ir(cod)Cl_2\}]$, 12.8 mol % chiral ligand (*R*)-**L2**, and 16 mol% $Zn(OTf)_2$ gave a 9/1 diastereomeric mixture of **72** in 73% yield and a 98/2 enantiomeric mixture of the major product of **72**. After conversion into epoxy ester **73** from **72** in four steps, γ-lactone **74** was obtained through the treatment of **73** with trifluoroacetic acid. The protection of the hydroxyl group of **74**, followed by Lemieux–Johnson oxidation, gave the aldehyde **75**, which was subjected to an alkylation reaction via an aldehyde enolate intermediate to construct a quaternary carbon center. This α-alkylation reaction of aldehyde was problematic due to the presence of the acidic proton ($pK_a \sim 20$) at the γ-lactone moiety. To achieve the direct α-alkylation of the aldehyde (the pK_a value of α-proton of the aldehyde is ~17), the chemoselective deprotonation was investigated using *t*-BuOK (the pK_a value of *t*-BuOH, which is the conjugate acid of *t*-BuOK is ~18).[32] The generation of the aldehyde enolate in the presence of *t*-BuOK at low temperatures, followed by treatment with methyl iodide and the gradual elevation of the temperature, gave **76** in a 36% yield. Finally, the synthesis of asperolide C (**61**) was achieved by the Pinnick oxidation of **76** and the sequential desilylation.

Yamamoto and co-workers reported that a complex **77**·$SnCl_4$ prepared from BINOL mono-ether **77** and Lewis acidic $SnCl_4$ catalyzed the enantioselective polyene cyclization to give **79** in 88% ee (Scheme 5).[29b] This complex was thought to work as a Brønsted acid. The acidic phenolic proton (the circled proton in the structure), the acidity of which increased due to chelation to $SnCl_4$, initiated the polyene cyclization reaction through the regio- and enantioselective protonation at the terminal olefin of **78**. This reaction proceeded even in the presence of catalytic amounts (0.2 equiv) of **77**·$SnCl_4$, although a decrease in the enantioselectivity was observed.

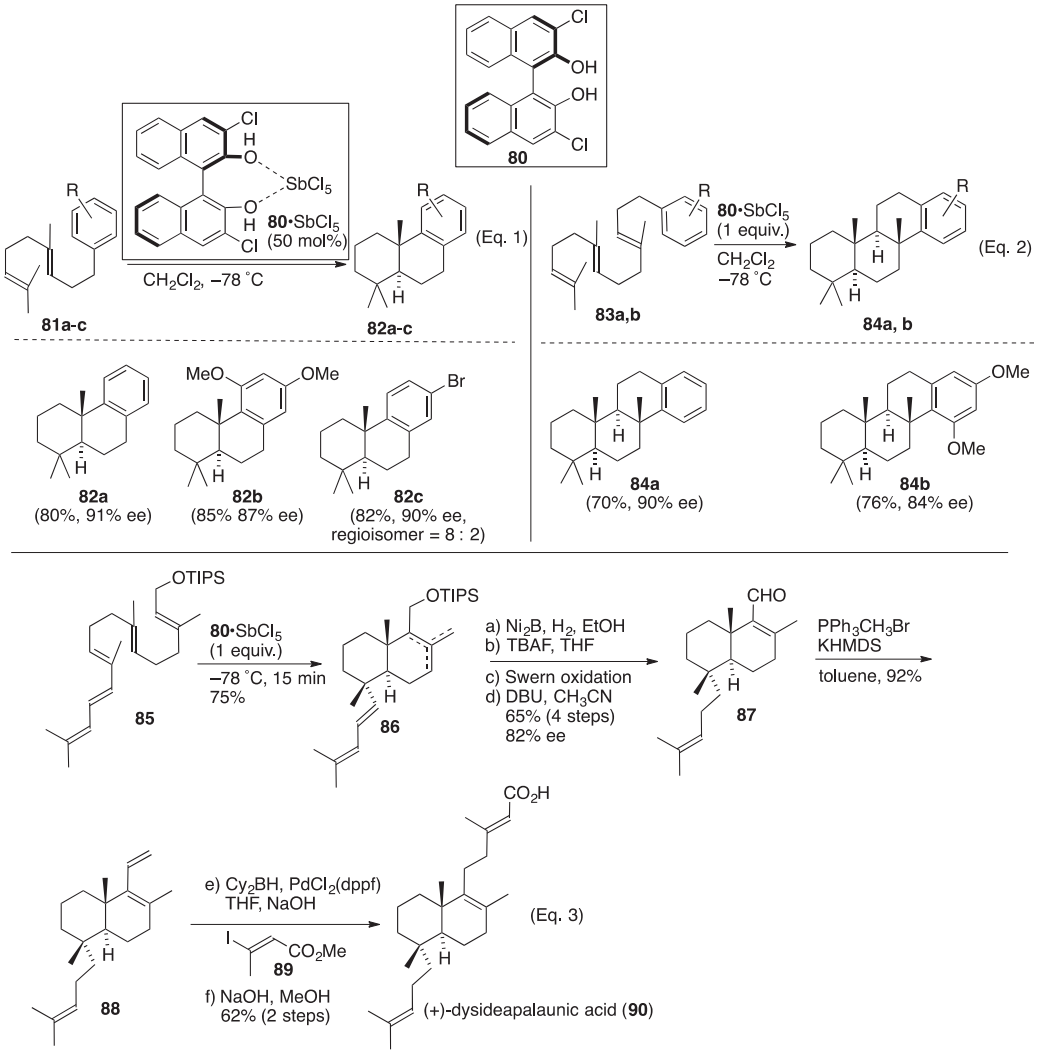
The enantioselectivity of the asymmetric polyene cyclization reaction was improved by Corey and co-workers through the development of a complex **80**·$SbCl_5$ prepared from the *o*,*o*′-dichloroBIONL **80** and $SbCl_5$, which provided a stronger Lewis acid compared to the $SnCl_4$ complex described by Yamamoto (Scheme 6).[33] The results of an investigation of the optimal conditions revealed that the cyclizations of **81a–81c** proceeded through the addition of 50 mol% **80**·$SbCl_5$ to give the bicyclic compounds **82a–82c** in up to 91% ee, respectively (Scheme 6, Eq. 1). Bicyclic compound **82c** was afforded as a mixture of the regioisomers because the cyclization proceeded at the *ortho*- or *para*-positions in bromobenzene. Next, tricyclization reactions were tried. The cyclization of **83a** and **83b** with 1 equiv of **80**·$SbCl_5$ gave the tricyclic compounds **84a** and **84b**, respectively, in high enantioselectivities (Scheme 6, Eq. 2). The use of **80**·$SbCl_5$ in the asymmetric polyene cyclization reaction improved the enantioselectivity and shortened the reaction time relative to the reaction time of **77**·$SnCl_4$. Corey's group applied these conditions to the total synthesis of a polycyclic terpenoid (Scheme 6, Eq. 3).[29d] The treatment of polyene **85** bearing five olefins with an equivalent amount of **80**·$SbCl_5$ gave bicyclic compound **86** as a mixture of three olefinic regioisomers in 75% yield and in 82% ee. This reaction proceeded through the regioselective protonation at the disubstituted olefin due to steric repulsion. Aldehyde **87** was prepared from **86** in four steps: regioselective hydrogenation at the disubstituted olefin via the P-2 nickel boride catalyst under a hydrogen atmosphere, desilylation, Swern oxidation, and isomerization of the olefin. Homologation of **87** via the Wittig reaction gave **88**, which yielded (+)-dysideapalaunic acid (**90**) via hydroboration, followed by a Suzuki coupling reaction with **89** and the hydrolysis of the methyl ester. Although the polyene cyclization reactions catalyzed by **80**·$SbCl_5$ are attractive,



Scheme 4. Enantioselective polyene cyclization (Eq. 1), strategy for the synthesis of asperolide C (**61**) (Eq. 2), and the total synthesis of asperolide C (**61**) using the enantioselective polyene cyclization induced by the allyliridium complex (Eq. 3).



Scheme 5. Enantioselective cyclization of **78** using complex (*S*)-**77**·$SnCl_4$ (Yamamoto's work).

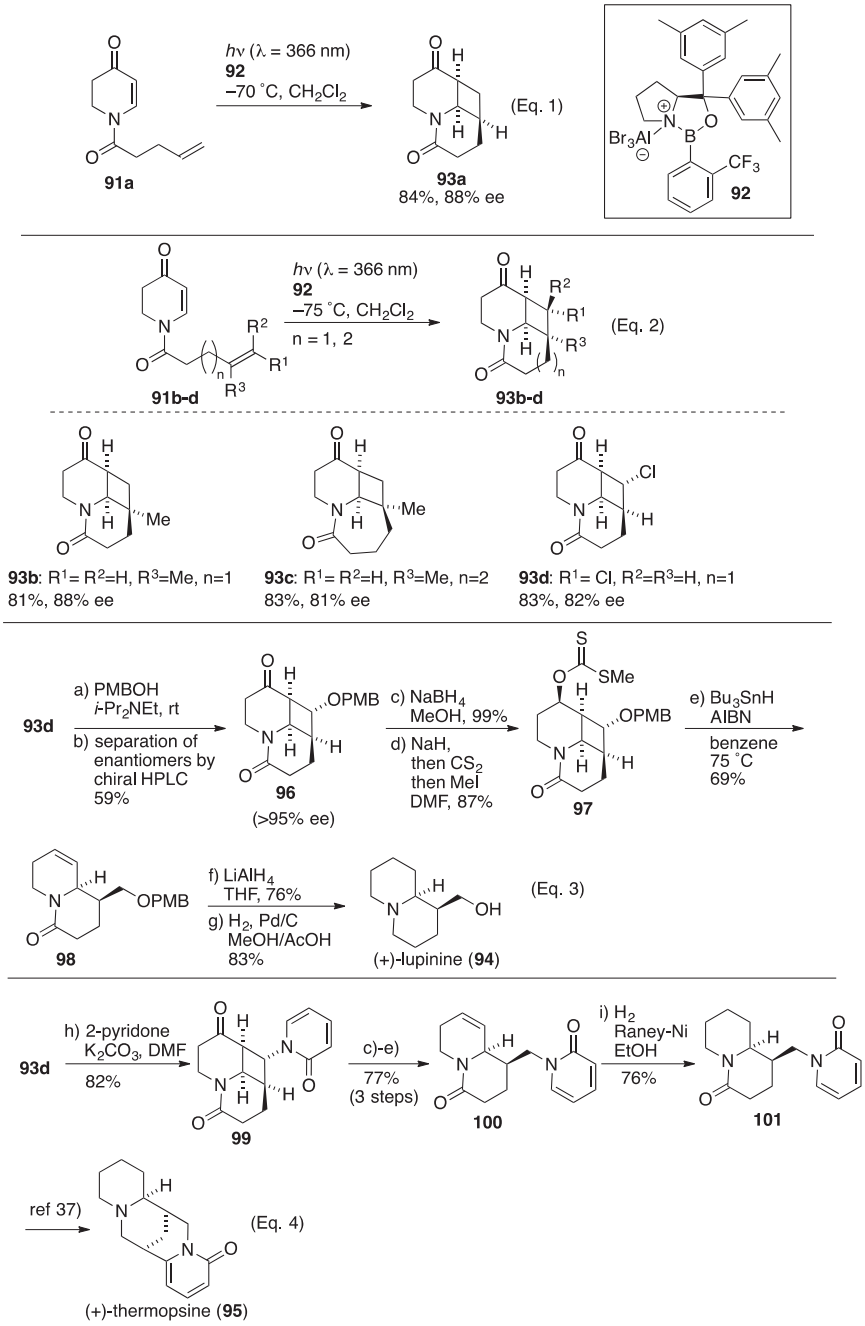


Scheme 6. Enantioselective bicyclization (Eq. 1) and tricyclization (Eq. 2) using the complex **80**·$SbCl_5$, and the total synthesis of (+)-dysideapalaunic acid (**90**) by the cationic double annulation reaction (Eq. 3).

decrease of loading amount of **80**·$SbCl_5$ is left as an important challenge.

Asymmetric synthesis of natural products through the catalytic [2+2]-photocycloaddition

Photoreactions have been employed recently in natural product synthesis.[34] In these reactions, the [2+2]-photocycloaddition (PCA) reaction between enones and olefins gives cyclobutanones, which are useful as synthetic intermediates due to their versatility with respect to chemical transformations.[35] After the [2+2]-PCA was initiated by the direct or photosensitizer-mediated excitation of enone from the ground state to the lowest excited triplet state, the excited enone underwent cycloaddition with olefin to give cyclobutanone via a 1,4-diradical intermediate. Bach and co-workers developed a catalytic asymmetric [2+2]-PAC of 5,6-dihydro-4-pyridones employing a chiral Lewis acid (Scheme 7, Eq. 1). The application of this reaction to alkaloid syntheses has been reported.[36] The UV spectrum of the 5,6-dihydro-4-pyridone **91a** in dichloromethane at a concentration of 0.5 mM showed a strong absorption at λ_{max} = 291 nm (molar absorption coefficient ε = 17,400) and a weak absorption at λ_{max} = 360 nm (ε = 70). On the other hand, whereas the UV spectrum of **91a** in the presence of a Lewis acid, such as ethylaluminum dichloride or boron trichloride, displayed a red shift in the strong absorption at λ_{max} = 343 nm (ε = 21,400) or at λ_{max} = 348 nm (ε = 24,200), respectively, a weak absorption was undetectable. These results indicate the possibility of asymmetric synthesis in the presence of a chiral Lewis acid via the selective excitation of complexes between **91a** and a Lewis acid. In other words, the irradiation of the [2+2]-PCAs at 419 nm or 366 nm in the presence of the catalyst **92** was investigated. Although irradiation of the [2+2]-PCA at 419 nm did not induce the reaction, the reaction proceeded cleanly at −70 °C upon irradiation at 366 nm under the optimal conditions to give **93a** in 84% yield and in 88% ee as the sole product. The concentration of the substrate and the purity of the solvent considerably affected the progress of the [2+2]-PCA reaction. The optimal concentration was determined to be 20 mM, and the solvent should be dehydrated and degassed. A decrease in the amount of the Lewis acid reduced the enantioselectivity. The scope and limitations of this reaction were investigated using a variety of substrates. Some results are shown in Scheme 7, Eq. 2. The 6-6 fused cyclic compound **93b** and the 6-7 fused cyclic compound **93c** containing a quaternary stereogenic center were obtained in 81% yield and 88% ee and in 83% yield and 81% ee, respectively, under the optimal conditions. This reaction was attractive because the chiral compound with a quaternary carbon center, such as **93b** and **93c** could provide a high yield and a high enantioselectivity. The chlorinated



Scheme 7. Chiral Lewis acid-catalyzed [2+2]-photocycloaddition (PCA) reaction (Eq. 1), its applications (Eq. 2), total synthesis of (+)-lupinine (**94**) (Eq. 3), and formal synthesis of (+)-thermopsine (**95**) (Eq. 4).

compound **91d** (R^1 = Cl) was also converted cleanly into **93d** in 83% yield and in 82% ee under the optimal conditions. Next, the synthesis of (+)-lupinine (**94**) and the formal synthesis of (+)-thermopsine from **93d** were investigated (Scheme 7, Eqs. 3 and 4). The conversion of **93d** into **96** through treatment with *p*-methoxybenzyl alcohol and diisopropylethylamine gave **96**, with an ee of up to 95% upon separation using chiral HPLC. Diastereoselective reduction of the ketone moiety in **96** gave secondary alcohol, which led to xanthate **97** through the sequential treatment of NaH, CS_2, and MeI. A ring-opening reaction of **97** was performed by treating with tributyltin hydride in the presence of AIBN to afford **98** in 69% yield. The release of the cyclic strain in cyclobutane drove this ring-opening reaction. The synthesis of (+)-lupinine (**94**) was accomplished from **98** through the reduction of the amide carbonyl, followed by deprotection of the PMB group and reduction of olefin under hydrogenolysis. Synthesis of (+)-thermopsine (**95**) was also commenced from **93d**. Treatment of **93d** with 2-pyridone under basic conditions in DMF gave **99**, which was delivered into quinolizidine **100** through the use of a sequence similar to those applied to obtain **98** from **96**. Finally, the formal synthesis of (+)-thermopsine (**95**) was achieved through the hydrogenolysis of **100** with Raney-Ni under a H_2 atmosphere to give **101**, which is an intermediate in the total synthesis of (±)-thermopsin, as reported by Gallagher.[37]

Conclusions

The recently reported catalytic asymmetric total syntheses of alkaloids and terpenoids were overviewed here. These attractive syntheses were achieved by employing the strategies developed

originally by each respective author based on catalytic asymmetric reactions. In addition to the total syntheses introduced in this review, enormous studies of catalytic asymmetric reactions have been reported. This area of research has become popular in the field of total synthesis. Certain reactions require some or a significant level of improvement; for example, the catalyst loading, enantioselectivity, and other features of the reaction should be significantly improved. With the development of new catalytic asymmetric reactions, we look forward to the future development of numerous new attractive and interesting asymmetric total syntheses based on novel strategies using chiral catalysts.

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